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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,615	01/20/2004	Avner Yayon	81408-4600	3532

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/761,615	YAYON ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *14-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-13 and 50, and of the various species in the reply filed on 5/16/05 is acknowledged. The traversal is on the ground(s) that the independent claims of Groups II-IV have been amended such that they depend from elected claim 1, and that claims 1-47 and 50 are drawn to a matrix and several preferred methods for making said matrix. This is not found persuasive because the process steps of claims 14, 23, and 34 do not necessarily produce the product of claim 1. Each of claims 14, 23, and 34 require calcium ions and an auxiliary agent, neither of which is required to be present in the composition of Group I. The products of Groups I-IV are distinct both physically and functionally, are not required one for the other, and are therefore patentably distinct.

The requirement is still deemed proper and is therefore made FINAL. Claims 14-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Examination will continue at this time on claims 1-13 and 50 ONLY, to the extent that they read on the elected species.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed with the WIPO on 7/18/02. It is noted, however, that applicant has not filed a certified copy of the PCT application as required by 35 U.S.C. 119(b).

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Israel on 9/19/01. It is noted, however, that applicant has not filed a certified copy of the Israeli application as required by 35 U.S.C. 119(b).

Applicant cannot rely upon the foreign priority papers to overcome the rejections herein because a copy and/or translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. **The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.**

The language should be clear and concise and should not repeat information given in the title. **It should avoid using phrases which can be implied**, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The use of the trademarks "CYQUANT", "HALOTEN", and "SNAKESKIN" has been noted in this application. These and all other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the

marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

Claim 1 is objected to because of the following informalities: It recites "anti fibrinolytic", which should read "anti-fibrinolytic". Claim 2 recites "mg protein", which should read "milligrams of protein" for clarity.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: A relationship between the claimed composition comprising fibrinogen, thrombin, and Factor XIII; and the requirement that said composition comprises at least 50% fibrin. The claim seems to be drawn to a composition in which the natural activities of thrombin and Factor XIII on fibrinogen are exploited to yield a composition comprising a crosslinked fibrin polymer, but the claim does not particularly point out that this is the case. It is not clear whether the composition is drawn to the starting products for said composition (*i.e.*, solutions

fibrinogen, thrombin, and/or Factor XIII) or to a composition in which all three components have reacted and some starting materials are residual therein. Clarification is required.

Claim 1 recites a matrix being "substantially devoid of organic chelating agents", which is confusing. The claim also recites a matrix having "substantially uniform pores", which is also confusing. In both cases, it is not particularly pointed out within the claim to what standard the invention should be compared. In addition, the claim recites a matrix having a "residual moisture below 3%". It is not clear to which process or timepoint the word "residual" refers. Clarification is required.

Because claims 2-13 and 50 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claims 3 and 4 are confusing because they recite plasma proteins that are "autologous", but no reference point is provided for said term. Clarification is required.

Claim 5 is confusing because it recites "tranexamic acid present in an amount of at least 5%" without pointing out whether this percentage is a weight percentage, a volume percentage, or some other type. Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seelich et al. (2003, U.S. Patent 6,548,729; reference A) taken in view of Wadström (1997, U.S. Patent 5,631,011; reference B), Wolfinbarger, Jr., et al. (2001, U.S. Patent 6,293,970; reference C), and Li (2000, U.S. Patent 6,090,996; reference D). The claims are drawn to a lyophilized biocompatible matrix comprising fibrinogen, thrombin, Factor XIII, and at least one anti-fibrinolytic agent. The claimed matrix comprises at least 50% fibrin by weight, has substantially uniform pores, is substantially devoid of organic chelating agents, and has a residual moisture less than 3%. In some

dependent claims, the anti-fibrinolytic agent is transexamic acid. In some dependent claims, the matrix further comprises an auxiliary component, specifically a polysaccharide, and more specifically hyaluronic acid. In some dependent claims, the matrix further comprises growth factors. In some dependent claims, the components are present in specific amounts. In some dependent claims, the matrix is useful for growing chondrocytes or progenitor cells.

Seelich et al. teach a fibrin sponge prepared by mixing fibrinogen, Factor XIII, and aprotinin with thrombin and calcium salt (Example 1, lines 42-62). The sponge of Seelich et al. is lyophilized (column 8, lines 31-35) and comprises 1.4 units of thrombin per cubic centimeter (Example 1). Seelich et al. further teach that the sponge may further comprise polysaccharides (column 3, lines 34-35), tranexamic acid (column 3, line 57), growth factors (column 3, line 60), and thrombin in a wide concentration range (column 3, lines 11-26). Seelich et al. teach that between 80% and 100% of the fibrin is cross-linked within their sponge (column 8, lines 49-50). The sponge of Seelich et al. can be used to culture mammalian cells, including chondrocytes (column 7, lines 59-62). Finally, Seelich et al. teach that the residual moisture of a lyophilized graft may be adjusted during or after lyophilizing said matrix (column 4, lines 37-44 and column 8, lines 31-41). Seelich et al. do not teach the use of hyaluronic acid, nor do they specifically exemplify a matrix having a residual moisture of 3% or less. Seelich et al. do not discuss the pore size or spacing of the matrix.

Wadström teaches a composition comprising fibrinogen, Factor XIII, and the anti-fibrinolytic agent aprotinin that can be mixed with thrombin, calcium ions, and sodium

hyaluronate to form a solid composition (Example 1). The composition of Wadström is biodegradable and biocompatible (column 3, line 15). Wadström further discloses that the composition may further comprise hyaluronic acid or other polysaccharides (column 1, lines 41-52). Wadström further discloses that tranexamic acid may be substituted for aprotinin (column 4, line 64).

Wolfinbarger Jr. et al. teach that freeze-dried tissue grafts contain less than about 5% residual moisture (column 11, lines 13-15).

A person of ordinary skill in the art would have had a reasonable expectation of success in adding hyaluronic acid to the sponge of Seelich et al. because Seelich et al. teach that polysaccharides may be included as stabilizers (column 3, lines 34-42). The skilled artisan would have been motivated to include hyaluronic acid because Wadström teaches that hyaluronic acid enhances the viscosity of biodegradable matrices (column 3, lines 52-58).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include the hyaluronic acid of Wadström in the sponge of Seelich et al. because Wadström exemplifies its use in the production of fibrin matrices (Example 1).

Seelich et al. teach adjusting the residual moisture of their lyophilized fibrin matrix to "at least 3%" (column 4, lines 39-40), it is logical to conclude that the residual moisture of said matrix before said adjusting step must be less than 3%. Wolfinbarger Jr., who teaches that lyophilized grafts contain less than about 5% residual moisture, provides further evidence of the veracity of this conclusion. Clearly, the selection of the

degree of residual moisture is a matter of routine optimization on the part of the skilled artisan, said artisan recognizing that lyophilized fibrin matrices have a residual moisture below 3% (according to Wolfinbarger Jr. et al. and Seelich et al.) and that the moisture of said matrices can be adjusted (according to Seelich et al.; column 4, lines 41-44). A holding of obviousness over the cited claims is therefore clearly required.

The selection of pore size and spacing clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Li teaches that porous implant materials can be made from fibrin (column 1, lines 15-26) and that the pore size and spacing within said material can be controlled by varying the density of the material and by controlling the speed of freezing and freeze-drying of the material (column 4, lines 48-51). A holding of obviousness over the cited claims is therefore clearly required.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SANDRA E. SAUCIER
PRIMARY EXAMINER

Lora E Barnhart

leb